REMARKS

Receipt of the Office Action of November 20, 2003 is acknowledged. Reconsideration of Claims 1-15 is respectfully requested in view of the above amendments and the following argument. Favorable consideration of new Claim 16 is also requested.

A. Section 102 Rejections

Claims 1, 2, 4-6 and 8 were rejected as anticipated by the Plowman et al reference (Lancet). The Examiner stated that the Lancet reference "teaches the parenteral administration of mesna to provide radioprotection at a dose of 400 mg/kg. The administration of mesna is associated with radiation therapy."

To anticipate a claim, the reference must teach every element of the claim. MPEP 2131. The Lancet reference fails this requirement, and the anticipation rejection should be withdrawn. The claims in issue require that treatment include the administration of an effective amount of the formula I compound to a human patient who has been exposed to ionizing radiation. The Lancet reference teaches that the administration of a single compound (mesna) within the formula I genus affords radioprotection at 400 mg/kg. No anticipation occurs because the Lancet reference fails to disclose administration to human patients, and further fails to disclose anything resembling an "effective" amount as claimed.

400 mg/kg (a dose of approximately 30 grams in an average person) of mesna administered to a human is not an effective dose- in humans, this amount would be a fatal dose. Mesna has been shown to be toxic in doses exceeding 2.4 g/m^2 in humans

(approximately a 4 gram total dose). The preferred dose of mesna, according to the Physician's Desk Reference (and also USPDI and AHFS) is 240 mg/m^2 (approximately 6 mg/kg).

Further, contrary to the examiner's statement that "The administration of mesna is associated with radiation therapy" mesna is not approved for use as a radioprotector, nor has approval for such use ever been sought. The Lancet reference concludes with a warning to clinicians that "this drug [mesna] should not be present at the time of TBI." *Emphasis added.*

Claims 1 and 4 were also rejected as anticipated by the van den Broeke, et al reference. Van den Broeke et al does not anticipate these claims, and the rejection must be withdrawn. The arguments above apply equally to the teachings of van den Broeke, et al. In addition, the Examiner's statement that "Van den Broeke teaches the administration of mesna for UV radiation protection" is incorrect and unsupported by the plain teachings of the reference. Van den Broeke, et al teaches a series of laboratory experiments to measure the effects of various thiols on photobinding of various compounds *in vitro*.

There is no teaching in van den Broeke, et al that mesna or any other thiol may be administered to a patient, and no guidance whatsoever regarding an effective amount to provide therapeutic treatment for radiation exposure. Van den Broeke, et al discloses laboratory experiments in an effort to establish a mechanism of action for radioprotection. The reference provides no teaching whatsoever that reads on, or is even relevant to claim 1 or claim 4. In addition regarding claim 4, Applicant did not note any teaching in the van den Broeke, et al reference that so much as alludes to parenteral administration of any compounds whatsoever.

B. Section 103 Rejections of Claims 1-13

Claims 1-15 were again rejected as obvious over the Lancet reference. Applicant reiterates the arguments advanced in the previously filed response, that the Examiner has incorrectly applied the limited teachings of the Lancet reference, and it is again respectfully submitted that no *prima facie* case of obviousness has been presented.

To establish a case of *prima facie* obviousness, the Examiner must fulfill three criteria: 1) There must be some suggestion or motivation in the reference or known to those skilled in the art to modify the reference; 2) a reasonable expectation of success; and 3) the prior art must teach each and every claim limitation. Further, these criteria must be found in the prior art, and cannot be taken from Applicant's disclosure. MPEP 2142.

With regard to Claims 1-4, the Examiner has never established a prima facie case of obviousness. The Lancet reference teaches that a 400 mg/kg intraperitoneal injection of mesna "significantly improved survival" of mice (no data is given to teach one what a "significant" survival improvement means in the reference), and that this dose (which would be lethal in humans) afforded 10% radioprotection.

The examiner also stated that "No quantitative component of therapy is recited in instant claims 1 and 5." Contrary to this statement, claims 1 and 5 provide for the administration of an "effective" amount of formula I compound according to the stated objective of the claimed method (treatment in claim 1, prophylaxis in claim 5). While not numerical, the term "effective amount" is a quantitative term understood by those skilled in the medical arts, and defined within the general ranges provided in the specification. To suggest

that the term "effective amount" is not quantitative is to ignore the plain language of the instant specification.

The examiner correctly notes that the Lancet reference teaches a 12 hour lapse between mesna administration and TBI, but then attempts to explain away this contrary teaching by an allusion to other sulfhydryl compounds (N-acetylcysteine) as being known radioprotective agents. No support for this statement was given by the examiner, nor are there currently any approved sulfhydryl agents that are approved for treatment or prophylaxis of the effects ionizing radiation. Mesna is approved only for use as a chemoprotectant for ifosfamide and cyclophosphamide. N-acetylcysteine is approved for use as a mucolytic agent, and as an antidote for acute acetaminophen overdose. No evidence exists that mesna or any similar sulfhydryl containing molecule has ever been administered to humans as a treatment or prophylaxis for the effects of ionizing radiation.

The Lancet reference was published 17 years ago. The publication states that Plowman, et al were "now looking at the route of administration and the timing and dose of mesna in respect of radioprotection achieved." However, a search conducted by Applicant's attorney disclosed no follow-up publications by Plowman et al regarding the results of any further research on mesna or similar sulfhydryl-containing compounds as radioprotectors. A span of 17 years with no additional publications on follow-up research actually supports the nonobviousness of the invention as fulfilling a long unmet need in the field. Graham v. John Deere, 383 U.S. 1, 148 USPQ 459 (1966).

Applicant is aware that amifostine, which is not a sulfhydryl-containing compound, and other non sulfhydryl-containing agents are currently undergoing human trials for use as a radioprotector, but none have yet been approved.

Applicant also takes issue with the examiner's conclusion that no more than routine experimentation would have been necessary to determine an optimal therapeutic dosage range, dosing regimen and route. As noted above, the Lancet reference dose (400 mg/kg) of mesna would be a lethal human dose of that agent. It can hardly be considered "routine" experimentation, when the original researchers were unable, after 17 years, to offer even a suggestion as to what a therapeutic or prophylactic radioprotective dose of mesna might entail.

C. Section 103 Rejections of Claims 14-15

With regard to Claims 14 and 15, the rejection of these claims is unjustified and not supported by evidence or by inference. The Examiner makes no specific reference to these claims at all, which is telling in that both Claims 14 and 15 define only formula I compounds that are not sulfhydryls. It is inconceivable that the Lancet reference even contemplated these compounds, much less teach their use.

Thioethers (where R_1 is lower alkyl), disulfides (where R_1 is -S-alkyl-R_4 and others), and conjugates (where R_1 is a sulfur-containing amino acid) are not even mentioned in the Lancet reference, nor in the current Office Action. There is no basis or justification for the rejection of Claims 14 and 15, nor has the examiner ever addressed the patentability of these claims.

Claims 14 and 15, as well as new claim 16 are clearly allowable.

In conclusion, all claims of the subject patent application are novel, and no *prima facie* case of obviousness has been established based on The Lancet reference. Favorable

reconsideration for claims 1-15 is respectfully solicited, and favorable consideration of new claim 16 is also solicited.

Respectfully submitted,

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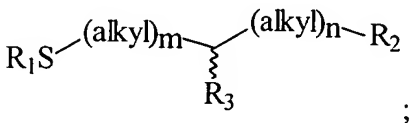
What Is Claimed Is:

1. (Currently Amended) A method of treating a patient for exposure to ionizing radiation, said method comprising administering to the patient an effective amount of a compound of formula I:

(I)



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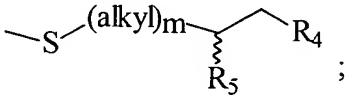
wherein:

R_1 is hydrogen, lower alkyl, a sulfur-containing amino acid or



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R_2 and R_4 are each individually $SO_3^-M^+$, $PO_3^{2-}M_2^{2+}$, or $PO_2S^{2-}M_2^{2+}$;

R_3 and R_5 are each individually hydrogen, hydroxy or sulfhydryl, where if R^1 is hydrogen, R^3 is not sulfhydryl;

m and n are individually 0, 1, 2, 3 or 4, with the proviso that if m or n is 0, then R_3 is hydrogen; and

M is hydrogen or an alkali metal ion; or

a pharmaceutically acceptable salt thereof.

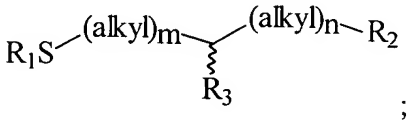
2. (Original) The method of Claim 1 wherein the effective amount of the formula I compound administered is from 0.1 mg/kg of body weight to 1,000 mg/kg of body weight.

3. (Original) The method of Claim 1 wherein the compound is administered orally.

4. (Original) The method of Claim 1 wherein the compound is administered parenterally.

5. (Original) A method of prophylactically treating a patient about to undergo radiation therapy, said method comprising administering to the patient prior to beginning a radiation therapy session, an effective amount of a compound of formula I:

(I)



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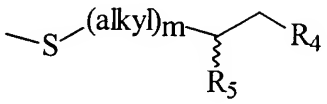
wherein:

R_1 is hydrogen, lower alkyl, a sulfur-containing amino acid or



;

R_2 and R_4 are each individually $SO_3^-M^+$, $PO_3^{2-}M_2^{2+}$, or $PO_2S^{2-}M_2^{2+}$;

R_3 and R_5 are each individually hydrogen, hydroxy or sulfhydryl, where if R^1 is hydrogen, R^3 is not sulfhydryl;

m and n are individually 0, 1, 2, 3 or 4, with the proviso that if m or n is 0, then R_3 is hydrogen; and

M is hydrogen or an alkali metal ion; or

a pharmaceutically acceptable salt thereof.

6. (Original) The method of Claim 5 wherein the effective amount of the formula I compound to be administered is 500 mg/m^2 to $40g/m^2$.

7. (Original) The method of Claim 5 wherein the formula I compound is administered to the patient at 15 minutes to 1 hour prior to beginning the radiation therapy session.

8. (Original) The method of Claim 5 wherein administration is by intravenous infusion.

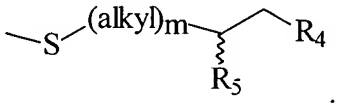
9. (Original) The method of Claim 5 wherein administration is oral.

10. (Original) The method of Claim 5 wherein an additional effective dose of formula I compound is administered about 2 hours after conclusion of the radiation therapy session.

11. (Original) The method of Claim 10 wherein additional effective doses are administered to the patient about every 4 hours after the first-mentioned additional effective dose.

12. (Original) The method of Claim 10 wherein the additional effective dose is administered orally.

13. (Original) The method of Claim 10 wherein the additional effective dose is administered by intravenous infusion.

14. (Original) The method of Claim 1 wherein R_1 is lower alkyl, a sulfur-containing amino acid or 

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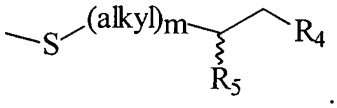
15. (Original) The method of Claim 5 wherein R_1 is lower alkyl, a sulfur-containing amino acid or 

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16. (New) The method of Claim 15 wherein the formula I compound to be administered is 2,2'-dithiobis ethane sulfonic acid, or a disodium salt thereof